BOX 313c
PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Eiichi IISHI et al.	Conf.:	
Appl. No.:	09/697,329	Group:	1624
Filed:	October 27, 2000	Examiner:	K. HABTE
For:	ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME		
Batch No.:	N32		

LETTER

Hand Carry to:
Petitions Office
Crystal Plaza 4
Room 3C-23
2201 South Clark Place
Arlington, Virginia 22202

Assistant Commissioner for Patents
Washington, DC 20231

March 20, 2002

Sir:

On March 19, 2002, Applicants' representative hand-carried to the Publishing Division: (1) an RCE; (2) Request for Consideration of Information Disclosure Statement; (3) Information Disclosure Statement (IDS) enclosing U.S. reference 2001/0051718 A1; and (4) two checks in the amounts of $130.00 and $740.00. Inadvertently, a Petition Under 37 C.F.R. §1.313(c)(2) was not enclosed with items (1)-(4). Attached to this Letter are: (A) copies of items (1)-(3); (B) a photocopy of the postcard receipt; and (C) the Rule 313(c)(2) Petition dated March 20, 2002.

Applicants respectfully request that the Petitions Branch consider the attached Petition in combination with items (1)-(4).

Applicants believe that the fees necessary for consideration of items (1)-(3) and the attached Petition have been paid in full; however, if necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Gerald M. Murphy, Jr. #43575 For
Gerald M. Murphy, Jr., #28,977

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/GMD/gh
1422-0449P

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BOX 313c
PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Eiichi IISHI et al.	Conf.:	
Appl. No.:	09/697,329	Group:	1624
Filed:	October 27, 2000	Examiner:	K. HABTE
For:	ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME		
Batch No.:	N32		

PETITION UNDER 37 C.F.R. § 1.313(c)(2)

Hand Carry to:
Petitions Office
Crystal Plaza 4
Room 3C-23
2201 South Clark Place
Arlington, Virginia 22202

BOX 313c
Assistant Commissioner for Patents
Washington, DC 20231

March 20, 2002

Sir:

This is a Petition to withdraw the above-mentioned application from Issue. The necessary fee under 37 C.F.R. § 1.17(h) of $130.00 was enclosed with the submission filed March 19, 2002 hand carried to the Publishing Division.

FACTS

1. The above-mentioned application has been allowed, and the Issue Fee was paid on January 10, 2002.

2. The applicants filed yesterday, March 19, 2002, a REQUEST FOR CONTINUED EXAMINATION (RCE) in order to submit an Information Disclosure Statement (copies are attached hereto).

REMEDY REQUESTED

It is requested that the above-mentioned application be withdrawn from Issue for consideration of an RCE under the provisions of 37 C.F.R. § 1.313(c)(2) and consideration of an Information Disclosure Statement under 37 C.F.R. § 1.97.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Gerald M. Murphy, Jr., #28,977 #43575 for

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/GMD/gh
1422-0449P

(Rev. 11/05/01)

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MAR 21 2002
PETITIONS OFFICE

Papers Filed herewith on: March 19, 2002 #41
DOCKET NO.: 1422-0449P ATTY.: GMM/6 MO
APPLICANT(S): Eiichi Ishi et al.
APPLN. NO: 09/687,329 FILED: 10-27-00
PAT NO.:

- ☐ New Application with Transmittal Letter
- ☐ Utility ☐ Design ☐ CIP ☑ PCT ☐ Provisional
- ☐ Filing Under 37 CFR 1.53(b) ☐ CONT ☐ DIV
- ☐ Filing Under 37 CFR 1.53(d) (CPA)
- ☐ Filing Under 37 CFR 1.114(RCE)
- ☐ Specification Consisting of: ____ pages
- ☐ Combined Declaration & Power of Attorney
- ☐ Assignment / Cover Letter
- ☐ Letter to Official Draftsman
- ☐ Drawings ____ Sheets ☐ Formal ☐ Informal ☐ Red-Ink
- ☐ Completion of Filing Requirements, PCT/DO/EO/905 or Formalities Letter and Executed Declaration
- ☐ Priority Document(s) / Cover Letter, No. Doc. ____
- ☐ Amendment: ____
  - ☐ Transmtl Ltr ☐ Large Entity ☐ Small Entity
- ☐ Response ____
- ☐ Information Disc Stmnt. PTO-1449(s) 1 ref(s)
- ☐ Notice of Appeal ☐ Appeal Brief
- ☐ Issue Fee Transmittal
- ☑ FEES: $740.00 chk 40228917
- ☐ Letter: $130.00 chk 40228918
- ☑ Other: Req. for Cons. of IDS Ret. Under 1.313

OIPE
MAR 19 2002
PATENT & TRADEMARK OFFICE

DOCKET NO. 1422-0449P

Receipt is hereby acknowledged of the papers filed as indicated in connection with the above identified case.
COMMISSIONER OF PATENTS AND TRADEMARKS
Due Date: March 19, 2002
Handcarry: Publishing Division: Crystal Park 3, Suite 910

HANDCARRY TO:
U.S. Patent and Trademark Office
Publishing Division
Crystal Park Three
Suite 910
2231 Crystal Park Drive
Arlington, VA 22202

COPY

PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Eiichi IISHI et al.	Conf.:	
Appl. No.:	09/697,329	Group:	1624
Filed:	October 27, 2000	Examiner:	K. HABTE
For:	ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME		

REQUEST FOR CONSIDERATION OF INFORMATION DISCLOSURE STATEMENT
(Submission with Filing of Continuation Application and Petition to Withdraw Parent Application from Issue)

Assistant Commissioner for Patents
Washington, DC 20231

March 19, 2002

Sir:

The following remarks are respectfully submitted in the above-identified application.

REMARKS

Claim 7 has been allowed in the present application and the Issue Fee was paid January 10, 2002.

Enclosed are:

1) a Petition under 37 C.F.R. § 1.313(c)(2);

2) a REQUEST FOR CONTINUED EXAMINATION (RCE); and

3) an Information Disclosure Statement (IDS).

The purpose of the Petition under 37 C.F.R. § 1.313(c)(2) is to withdraw the application from issue and allow the Examiner to consider a REQUEST FOR CONTINUED EXAMINATION (RCE) and an

P.O. Box 747
Falls Church, Virginia 22040-0747
Phone: (703) 205-8000
Fax: (703) 205-8050
(703) 698-8590 (GIV)

Birch, Stewart, Kolasch & Birch, LLP

Fax

FAX RECEIVED

MAR 2 1 2002

PETITIONS OFFICE

To:	Daniel Belzer Petitions Office	**From:**	Garth M. Dahlen, Ph.D.
Fax:	703-308-6916	**Date:**	March 21, 2002
Phone:	703-305-9282	**Pages:**	26 (including cover sheet)
Your Ref.:		**Our Ref.:**	1422-0449P
Re:	Serial No.: 09/697,329	**CC:**	

☒ **Urgent** ☒ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Comments: **On March 20, 2002, Applicants' representative hand-carried the enclosed documents to the Patent Office. Unfortunately, the documents were hand-carried to Art Unit 1600 by accident, as evidence by the enclosed stamped postcard receipt. Applicants respectfully request that the Petitions Branch consider the attached documents.**

Information Disclosure Statement (IDS) not previously filed in the application.

Should there be any outstanding matters which need to be resolved in the present application, the Examiner is respectfully requested to contact Garth M. Dahlen, Ph.D. (Reg. No. 43,575) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____ #43575
Gerald M. Murphy, Jr., #28,977
for

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

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1422-0449P

Enclosures: IDS, RCE and Petition under 37 C.F.R. § 1.313(c)(2)

(Rev. 02/20/02)

COPY

BOX RCE
PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Eiichi IISHI et al. Conf.:

Appl. No.: 09/697,329 Group: 1624

Filed: October 27, 2000 Examiner: K. Habte

For: ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME

HANDCARRY TO:
U.S. Patent and Trademark Office
Publishing Division
Crystal Park Three
Suite 910
2231 Crystal Park Drive
Arlington, VA 22202

REQUEST FOR CONTINUED EXAMINATION UNDER 37 C.F.R. § 1.114

FAX RECEIVED
MAR 2 1 2002
PETITIONS OFFICE

BOX RCE
Assistant Commissioner for Patents
Washington, DC 20231

March 19, 2002

Sir:

This is a "Request for Continued Examination" under 37 C.F.R. § 1.114, the provisions of which do not apply to:

(1) A provisional application; (2) An application for a utility or plant patent filed under 35 U.S.C. 111(a) before June 8, 1995; (3) An international application filed under 35 U.S.C. §363 before June 8, 1995; (4) An application for a design patent; or (5) A patent under reexamination.

Submission of an RCE is limited to an application in which prosecution is closed; e.g. final rejection, Ex Parte Quayle; or notice of allowability

☒ This Request for Continued Examination is being filed prior to the earliest of:

(1) Payment of the issue fee, unless a petition under § 1.313 is granted; (2) Abandonment of the application; or (3) The filing of a notice of appeal to the U.S. Court of Appeals for the Federal Circuit under 35 U.S.C. § 141, or the commencement of civil action under 35 U.S.C. §§ 145 or 146, unless the appeal or civil action is terminated.

☐ The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. § 1.8.

☐ The enclosed document is being transmitted via facsimile.

☒ **Submission Required under 37 C.F.R. § 1.114:**

Enter as part of the present submission:

☐ An After Final Amendment previously filed on , under 37 C.F.R. § 1.116 but unentered, in the present application.

☐ Arguments in the Appeal Brief or Reply Brief previously filed on .

☐ A Reply Under Rule 1.111, attached hereto. Claim fee(s) are calculated as set forth below:

	TOTAL NUMBER OF CLAIMS PREVIOUSLY PAID FOR	TOTAL NUMBER OF CLAIMS BEING FILED HEREWITH	NUMBER EXTRA	Large Entity		Small Entity	
				Rate	Fee	Rate	Fee
Total Claims	20			X 18	$	X 9	$
Independent Claims	3			X 84	$	X 42	$
			TOTAL CLAIM FEE(S)			$0.00	

☒ An Information Disclosure Statement (IDS) and PTO-1449 form(s) is/are attached hereto for the Examiner's consideration.

☐ Other:

☐ **Miscellaneous**

☐ Suspension of action on the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of ( ) months. (Period of suspension shall not exceed 3 months.)

☒ **Fees**

The required fee under 37 C.F.R. § 1.17(e) as required by 37 C.F.R. § 1.114 when the RCE is filed, is enclosed herewith:

☐ $370.00 - small entity

Appl. No. 09/697,329

☒ $740.00 - large entity

☐ The applicant(s) hereby petition(s) for an extension of ( ) month(s) pursuant to 37 C.F.R. §§ 1.17 and 1.136(a). The fee has been calculated as shown below:

☐ NO extensions of time have been previously obtained in the prior application. Thus, a fee of $0.00 is required for the full period of the above-requested extension of time.

☐ An extension of ( ) month(s) was previously requested and paid for on in the instant application. Thus, a fee of $0.00 is required to obtain an additional ( ) month(s) extension.

☐ The fee of $130.00 under 37 C.F.R. § 1.17(i) for suspension of action is enclosed.

☒ Enclosed is(are) check(s) in the total amount of $740.00 for the applicable filing fee, additional claims fee, suspension fee, and/or extension fees.

☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this sheet is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Gerald M. Murphy, Jr. #43575
Gerald M. Murphy, Jr., #28,977 for

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/GMD/gh
1422-0449P

Attachments

(Rev. 02/12/02)

HANDCARRY TO:
U.S. Patent and Trademark Office
Publishing Division
Crystal Park Three
Suite 910
2231 Crystal Park Drive
Arlington, VA 22202

COPY

PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Eiichi IISHI et al. Conf.:

Appl. No.: 09/697,329 Group: 1624

Filed: October 27, 2000 Examiner: K. HABTE

For: ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME

INFORMATION DISCLOSURE STATEMENT
(SUBMISSION AFTER FILING OF AN APPLICATION BUT BEFORE FINAL REJECTION OR NOTICE OF ALLOWANCE OR CONCURRENTLY WITH A RULE 53(d) CPA APPLICATION OR WITH A RULE 1.114 RCE APPLICATION)

Assistant Commissioner for Patents
Washington, DC 20231

March 19, 2002

Sir:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications, or other information submitted for consideration by the Office are listed on the PTO-1449(s), attached hereto.

II. COPIES (check at least one box)

a. ☒ Submitted herewith is a legible copy of (i) each U.S. and foreign patent; (ii) each publication or that portion which caused it to be listed; and (iii) all other information or that portion which caused it to be listed.

b. ☐ Some or all of the documents listed on the PTO-1449 are not enclosed because they were cited in the International Search Report and copies should already be in the PTO file. If copies are needed, please contact the undersigned.

III. CONCISE EXPLANATION OF THE RELEVANCE
(check at least one box)

a. ☒ **DOCUMENTS IN THE ENGLISH LANGUAGE**

The attached patents, publications, or other information in the English language do not require a statement of relevancy.

b. ☐ **DOCUMENTS NOT IN THE ENGLISH LANGUAGE**

A concise explanation of the relevance of all patents, publications, or other information listed that is not in the English language is as follows:

c. ☐ **ENGLISH LANGUAGE SEARCH REPORT**

An English language version of the search report or action that indicates the degree of relevance found by the foreign office is attached, thereby satisfying the requirement for a concise explanation. See MPEP 609(A)(3).

d. ☐ **OTHER**

The following additional information is provided for the Examiner's consideration.

FEES

IV. ☐ THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(b): (check one box)

a. ☐ within three months of the filing date of a national application (37 C.F.R. § 1.97(b)(1)). No fee or statement is required. (This section is not to be used with RCE's and CPA's).

b. ☐ within three months of the date of entry of the national stage as set forth in § 1.491 in an international application (37 C.F.R. § 1.97(b)(2)). No fee or statement is required.

c. ☒ concurrently with the filing of a Continued Prosecution Application under 37 C.F.R. § 1.53(d) or concurrently with the filing of a Request for Continued Examination under § 1.114 (37 C.F.R. § 1.97(b)(4)). No fee or statement is required.

d. ☐ before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b)(3)). No fee or statement is required.
In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the statement under 37 C.F.R. § 1.97(e) below, or, if no statement has been made, charge our deposit account in the amount of $180.00 as required by 37 C.F.R. § 1.17(p).

V. ☐ THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(c): (check one box)

before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c)(1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c)(2)).

a. ☐ No statement; therefore, a fee in the amount of $180.00 as required by 37 C.F.R. § 1.17(p).

or

b. ☐ See the statement below. No fee is required.

VI. STATEMENT UNDER 37 C.F.R. § 1.97(e) (check only one box)

The undersigned hereby states that

a. ☐ each item of information contained in the IDS was first cited in any communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

b. ☐ no item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of IDS was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the IDS.

c. ☐ Some of the items of information were cited in a communication from a foreign Patent Office. As to this information, the undersigned states that each item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS. As to the remaining information, the undersigned hereby states that no item of this remaining information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application and, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

VII. PAYMENT OF FEES (check one box)

☐ A check in the amount of $180.00 as required by 37 C.F.R. § 1.17(p) is enclosed for the above-identified fee.

☐ Please charge Deposit Account No. 02-2448 in the amount required by 37 C.F.R. § 1.17(p) for the above-indicated fee. A triplicate copy of this paper is attached.

☐ No fee is required.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is requested to consider this IDS under the proper rule and charge the appropriate fee to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Gerald M. Murphy, Jr. #43575
Gerald M. Murphy, Jr., #28,977 for

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/GMD/gh
1422-0449P

Enclosures:
- ☒ PTO-1449
- ☒ Documents
- ☐ Foreign Search Report
- ☐ Fee
- ☐ Other:

(Rev. 10/31/01

Sheet 1 of 1 ( )

Form PTO-1449

INFORMATION DISCLOSURE CITATION IN AN APPLICATION

(Use several sheets if necessary)

ATTY DOCKET NO.	APPLICATION NO.
1422-0449P	09/697,329
APPLICANT: Eiichi ISHII et al.	
FILING DATE: October 27, 2000	GROUP: 1624

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE
	2001/0051718 A1	2001-12-13	Singer et al.			

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (Include Name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

20010051718A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2001/0051718 A1

Singer et al. (43) Pub. Date: Dec. 13, 2001

(54) NOVEL SYNTHESIS AND CRYSTALLIZATION OF PIPERAZINE RING-CONTAINING COMPOUNDS

(76) Inventors: Claude Singer, Kfar Saba (IL); Anita Liberman, Tel Aviv (IL); Nina Finkelstein, Herzliya (IL)

Correspondence Address:
KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004 (US)

(21) Appl. No.: 09/900,646

(22) Filed: Jul. 6, 2001

Related U.S. Application Data

(60) Division of application No. 09/552,485, filed on Apr. 18, 2000, which is a non-provisional of provisional application No. 60/130,047, filed on Apr. 19, 1999.

Publication Classification

(51) Int. Cl.[7] C07D 487/22

(52) U.S. Cl. 540/577

(57) ABSTRACT

The present invention is directed to methods for the preparation of piperazine ring-containing compounds, particularly mirtazapine. According to the present invention, the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine is made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with a base where the base is present in a ratio of up to about 12 moles of the base per one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine. The mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with potassium hydroxide at a temperature of at least about 130° C. The method of the present invention also includes reacting 2-amino-3-hydroxymethyl pyridine with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl piperazine, and adding sulfuric acid to the 1-(3-hydroxymethylpyridyl-2)-phenyl-4-methylpiperazine to form mirtazapine. The present invention also relates to new processes for recrystallization of mirtazapine from crude mirtazapine.

NOVEL SYNTHESIS AND CRYSTALLIZATION OF PIPERAZINE RING-CONTAINING COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

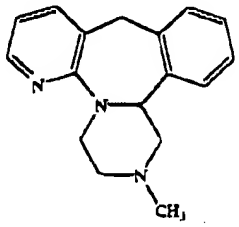
[0001] This application claims the benefit of U.S. Provisional Application No. 60/130,047, filed Apr. 19, 1999.

FIELD OF THE INVENTION

[0002] The present invention relates to synthetic organic chemistry, particularly, to synthesis of piperazine ring-containing compounds, such as mirtazapine, and to the crystallization of mirtazapine from different solvents and solvent systems.

BACKGROUND OF THE INVENTION

[0003] Mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a]pyrido[2,3-c][2] benzazepine, having the formula I:

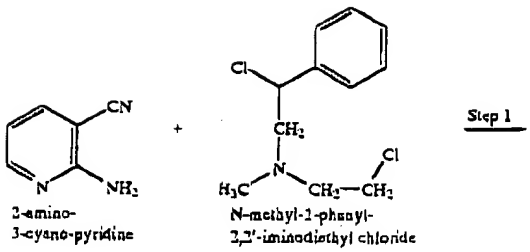


I

[0004] is approved, under the trademark Remeron®, by the U.S. Food and Drug Administration, for the treatment of depression. Mirtazapine has a tetracyclic chemical structure unrelated to other classes of antidepressants such as selective serotonin reuptake inhibitors, tricyclics or monoamine oxidase inhibitors. Mirtazapine belongs to the piperazinoazepine group of compounds.

[0005] Mirtazapine may be made by methods described in U.S. Pat. No. 4,062,848. By a process of U.S. Pat. No. 4,062,848 ("the '848 patent"), the mirtazapine intermediate 1-(3-hydroxymethylpyridyl-2-4-methyl-2-phenyl-piperazine is made by a three step process starting with a 2,3-substituted pyridine derivative. Therefore, as shown in Scheme 1, when starting with 2-amino-3-cyano-pyridine, the process of the '848 patent requires four synthetic steps to make mirtazapine. It is desirable to have a process for making mirtazapine that requires fewer steps, and therefore requires less reagent, solvent and time.

Scheme 1

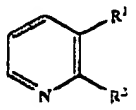


[0006] By the process of U.S. Pat. No. 4,062,848 ("the 848 patent"), the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine is made by the hydrolysis of the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine under highly basic conditions of 25 moles of potassium hydroxide (KOH) per mole of nitrile, at high temperature and for long reaction times of 24 hours. These harsh reaction conditions necessitate a great effort in purifying the resulting product as well as creating environmental waste disposal issues associated with neutralizing and disposing of large volumes of concentrated basic solutions. The highly basic conditions and long reaction times make the procedure of the '848 patent very costly, especially in terms of reactor time.

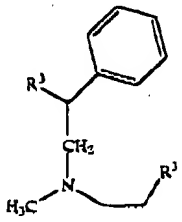
[0007] According to the methods of U.S. Pat. No. 4,062,848, crude mirtazapine is recrystallized only in ether and petrol ether 40-60. The solvents ether and petrol ether 40-60 are both very difficult to handle in large scale production.

SUMMARY OF THE INVENTION

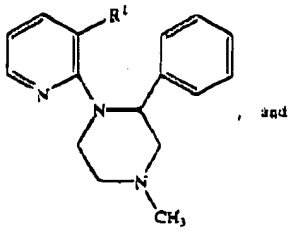
[0008] The present invention is directed to a method for the preparation of mirtazapine, comprising the steps of: reacting a compound of the formula



[0009] with a compound of the formula

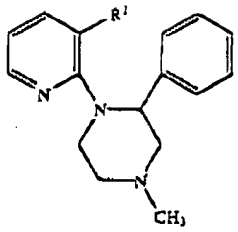


[0010] to form a compound of the formula



, and

[0011] adding a ring closing reagent to the compound of the formula



[0012] to form mirtazapine, wherein R^1 is selected from the group consisting of hydroxymethyl, chloromethyl, bromomethyl and iodomethyl; R^2 is amine; and R^3 is selected from the group consisting of chloro, fluoro, bromo and iodo.

[0013] In a preferred embodiment of the present invention is directed to a method for the preparation of mirtazapine, comprising the steps of reacting 2-amino-3-hydroxymethyl pyridine with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl piperazine, and adding sulfuric acid to the 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine to form mirtazapine.

[0014] Further, it has now been discovered that the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine may be made by hydrolysis of the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine using new more favorable reaction conditions. The new reaction conditions of the present invention include a low mole to mole ratio of potassium hydroxide to nitrile and shorter reaction times.

[0015] The present invention relates to a improved process for making 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine comprising the step of reacting 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with a base wherein the base is present in a ratio of up to about 12 moles of the base per one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine.

[0016] In a preferred embodiment of the present invention, the ratio of the base to 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is about 12 moles of base to about one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine to about 9 moles of base to about one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine.

[0017] In another preferred embodiment of the present invention, the base is potassium hydroxide or sodium hydroxide.

[0018] In another embodiment of the present invention, the mixture of the 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine and the base is heated to at least about 130° C.

[0019] In another embodiment of the present invention, the hydrolysis of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is carried out in a mixture water and a solvent selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, dimethylformamide, dimethylacetamide and dimethylsulfoxide.

[0020] The present invention also relates to improved processes for making mirtazapine from crude mirtazapine

comprising the steps of (a) heating a mixture of crude mirtazapine and solvent; and (b) isolating mirtazapine.

[0021] In a preferred embodiment of the present invention, water is added to the heated mixture of mirtazapine and solvent to facilitate precipitation of mirtazapine.

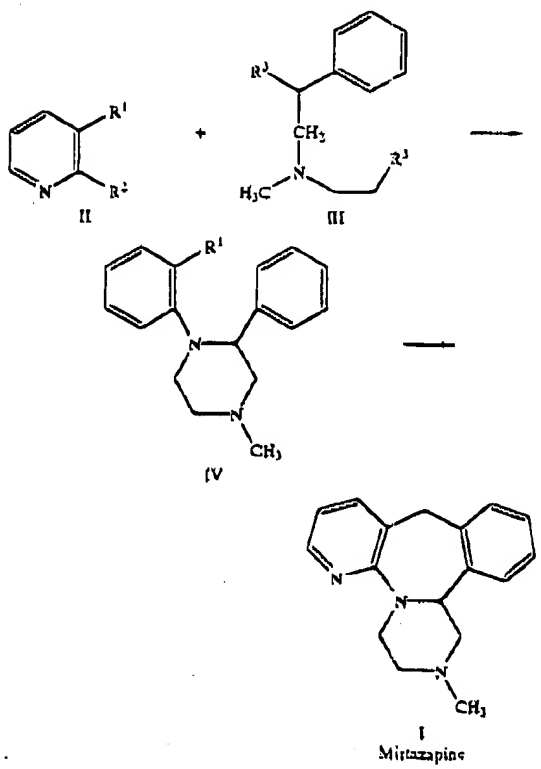
[0022] In an additional embodiment of the present invention, preferred solvents are methanol, ethanol, isopropanol, acetone, toluene, and hexane and mixtures thereof.

[0023] In an additional embodiment of the present invention, preferred solvents are toluene, hexane, and methylene chloride.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention relates to a novel process for preparing piperazine ring-containing compounds, such as mirtazapine, as described in Scheme 2 below. The process of the present invention is advantageous over prior art processes due to, inter alia, the higher yield, smaller number of steps in relation to the alternative methods, and minimized raw material costs.

Scheme 2



[0025] More particularly, the present invention relates to the process of making mirtazapine from compounds of the formulae II, III and IV. In the process of the present invention the compound of formula II in Scheme 2 above, wherein R^1 denotes hydroxymethyl, chloromethyl, bromomethyl or iodomethyl, and R^2 denotes amine, preferably $-NH_2$, is reacted with the compound of formula III in Scheme 2 above, wherein R^3 denotes chloro, fluoro, bromo or iodo, to form the compound of formula IV wherein R^1 is defined as above.

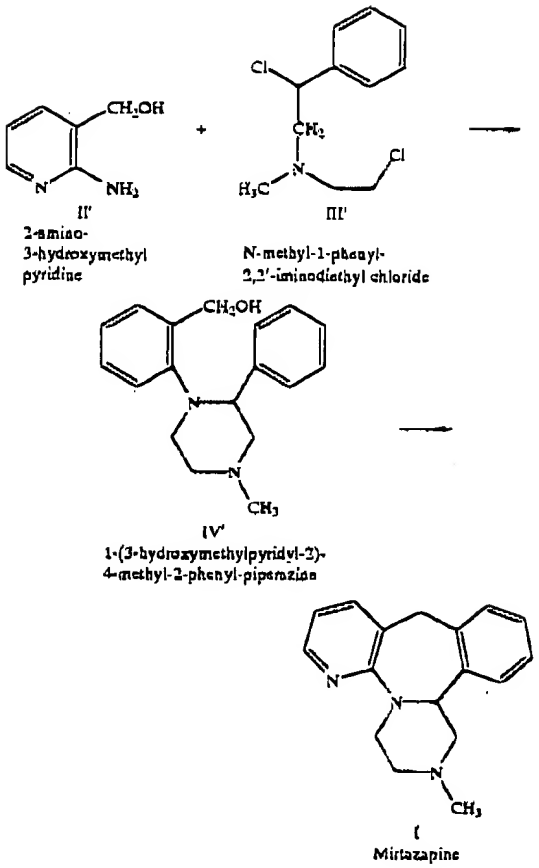
[0026] In the process of the present invention, the compound of formula II is dissolved in a solvent such as methylene chloride. The compound of formula III is added to the solvent mixture and the resulting mixture is heated. Preferably the reaction mixture is heated to the reflux temperature of the solvent. The mixture is heated to form the compound of formula IV. Mirtazapine is then prepared by ring closure of the compound of formula IV. Ring closure of the compound of formula IV may be performed using a ring-closing reagent. Suitable ring closing reagents are dehydrating or dehydrohalogenating agents. Dehydrating or dehydrohalogenating agents that may be added to the reaction mixture for this purpose include acids, such as sulfuric acid, concentrated sulfuric acid, concentrated hydrochloric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid (PPA), phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide and Lewis acids, such as aluminum chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride.

[0027] Dehydrating agents that are particularly preferred are sulfuric acid and phosphorus derivatives, such as PPA and phosphorus oxychloride. Concentrated sulfuric acid most preferred. A particularly preferred dehydrohalogenating agent is aluminum chloride.

[0028] In a preferred embodiment of the present invention the compounds of the formulae II, III and IV are compounds of the formulae II', III' and IV' respectively as shown in Scheme 3 below. In an embodiment of the present invention, 2-amino-3-hydroxymethyl pyridine is reacted with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine. In the present invention, 2-amino-3-hydroxymethyl pyridine (II') is added to a solvent. Suitable solvents include 1,2-dichloroethane, methylene chloride, dimethylformamide, dimethylacetamide and dimethylsulfoxide. N-Methyl-1-phenyl-2,2'-imidodiethyl-chloride (III') is added to the solvent mixture and the resulting mixture is heated. Preferably the reaction mixture is heated to the reflux temperature of the solvent. The mixture is heated until 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine is formed and the reaction is complete. A suitable time is about six to about 24 hours. The 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine is then converted to mirtazapine by ring closure.

[0029] The ring closure of 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine is performed under strongly dehydrating (R^1=OH) conditions, preferably at an elevated temperature. Suitable dehydrating agents, include acids, such as sulfuric acid, concentrated hydrochloric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid (PPA), phosphorus oxychloride, phosphorus trioxide and phosphorus pentoxide. Dehydrating agents that are particularly preferred are sulfuric acid and phosphorus derivatives, such as PPA and phosphorus oxychloride. Concentrated sulfuric acid is most preferred.

Scheme 3



[0030] The present invention also provides new processes for making the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine from the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine where the nitrile is (I) hydrolyzed by base using a new low mole to mole ratio of base to the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine and (ii) hydrolyzed using short reaction times.

[0031] Where the present invention provides improved methods for making the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine, the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is dissolved in a mixture of water and organic solvent. Preferred organic solvents include polar aprotic solvents and alcohols. Polar aprotic organic solvents such as dimethylformamide, dimethylacetamide and dimethylsulfoxide and the like are preferred. Preferred alcohols are methanol, ethanol, propanol, isopropanol, butanol and the like. A suitable amount of base, such as potassium hydroxide or sodium hydroxide, is added to the reaction mixture. An amount of base, such as potassium hydroxide or sodium hydroxide, of up to about 12 moles of base per mole of nitrile (for example 12:1 KOH:nitrile) is preferred. Amounts of base, such as potassium hydroxide, in the ratio of about 9 moles of potassium hydroxide per one mole of nitrile (9:1 KOH:nitrile), to about 12 moles of potassium hydroxide per mole of nitrile (12:1 KOH:nitrile) are preferred.

[0032] In the present invention, the mixture of the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine, solvent and base is heated to at least about 130° C. Reaction temperatures of about 130° C. to about 150° are preferred. In an embodiment of the present invention, the reaction may be conducted under pressure to facilitate the attainment of high temperatures. A pressure of at least about 3 atmospheres is preferred. Pressures of at least about 3 atmospheres to about 4 atmospheres are more preferred. The reaction mixture is heated until the reaction is complete. The completion of the reaction may be monitored by HPLC. The amount of time needed for the completion of the hydrolysis of the nitrile varies with the temperature of the reaction. Higher reaction temperatures generally require shorter reaction times, while lower reaction temperatures generally requires longer reaction times. While not limiting the reaction time of the present invention, preferred reaction times of the present invention may be from about 2 hours to about 8 hours. Upon completion of the reaction, the pH of the reaction mixture is lowered, preferably to a pH of about 6 to about 7. Preferably the pH is lowered with hydrochloric acid. The mirtazapine intermediate, 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is isolated following washing and filtration of the reaction mixture.

[0033] In an additional embodiment of the present invention, the reaction mixture of the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine, and potassium hydroxide, is heated while using a minimum amount of water, such as about 0.25-1 mL of water per gram of KOH, and small amounts of an aprotic solvent such as dimethylformamide, dimethylacetamide and dimethylsulfoxide, such as about 0.1 to 0.5 grams of aprotic solvent per gram of nitrile, under very concentrated conditions or almost neat conditions at atmospheric pressure. The mirtazapine intermediate, 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is isolated following washing and filtration of the reaction mixture.

[0034] The new processes of the present invention for making the mirtazapine intermediate 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine from the nitrile 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine, significantly reduce the quantity of potassium hydroxide used, from 25 moles of potassium hydroxide per mole of the nitrile as in the '848 patent, to about 12 moles or less of potassium hydroxide to one mole of the nitrile. The reduction in the amount of base needed considerably simplifies the work-up of the reaction and minimizes environmental problems.

[0035] The present invention also provides new methods for making pure mirtazapine by purifying crude mirtazapine by recrystallization. Upon the ring closure of 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine to form mirtazapine, the crude product, mirtazapine, is purified by recrystallization.

[0036] It has been discovered that common solvents such as toluene or methylene chloride and solvent systems such as alcohol-water can be used in the recrystallization of crude mirtazapine. According to the present invention, crude mirtazapine is suspended in a suitable solvent. Preferred solvents include methanol, ethanol, isopropanol, and acetone and mixtures thereof, or mixtures of one or more of those

solvents with water. Additional preferred solvents also include toluene, hexane, and methylene chloride. Solvent mixtures of water and ethanol are more preferred. Solvent mixtures of ratios of about 1:1 to about 1:4 ethanol:water are preferred.

[0037] In the present invention, the suspension of crude mirtazapine and solvent is heated to a suitable temperature. Suitable temperatures include, for example, the reflux temperature of the solvent system being used in any particular embodiment of the present invention. For example, in an embodiment of the present invention where toluene is the solvent, a temperature of about 110° C. is suitable. Purified mirtazapine precipitates upon cooling of the reaction mixture. Filtration and drying of the resulting precipitate yields purified, recrystallized mirtazapine.

[0038] In a further example, crude mirtazapine is suspended in a solvent such as ethanol, and the mixture is heated to reflux. Water is then added dropwise and the solution is cooled to facilitate precipitation of mirtazapine. The precipitate is purified by filtration, washing and drying to yield purified mirtazapine. The crystallized mirtazapine may be a water adduct thereby containing up to 3% water by weight (3% w/w).

[0039] The solvents and solvent systems of the present invention are suitable for large scale reactions, and are more suitable for large scale reactions than ether or petrol ether 40-60. Additionally, the crystallization yield can be substantially improved when using the solvent system of the present invention.

[0040] Mirtazapine and mirtazapine intermediates, 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine and 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine each contain an asymmetric carbon atom, as a result of which separate optical isomers may be prepared in addition to a racemic mixtures. Processes of the present invention include these optical isomers just as the racemic mixtures are included in the invention.

[0041] In accordance with the present invention, mirtazapine produced by the process of the present invention may be prepared as pharmaceutical compositions that are particularly useful for the treatment of depression. Such compositions comprise a therapeutically effective amount of mirtazapine with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

EXAMPLES

[0042] The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

Example 1

Preparation of 1-(3-Hydroxymethylpyridyl-2)-4-Methyl-2-Phenyl-Piperazine

[0043] In a 50 mL three-necked flask equipped with a mechanical stirrer, a condenser and a thermometer 1 g (0.008 mole) of 2-amino-3-hydroxymethyl pyridine and 20 mL of 1,2-dichloroethane were charged. The mixing is started and to the suspension 2.8 g (0.012 mole) of N-methyl-1-phenyl-2,2'-iminodiethyl-chloride are added. The reaction mixture is heated to reflux (~80° C.) and maintained at this temperature for six hours.

[0044] After six hours the reaction mixture is cooled and the solvent (1,2-dichloroethane) is removed by dry distillation. A yellowish powder is obtained which contains 1.8 g 1-(3-hydroxymethyl pyridyl-2)-4-methyl-2-phenyl-piperazine (yield 80%). This powder can be used without additional purification for the preparation of mirtazapine.

Example 2

Preparation of Mirtazapine

[0045] In a 50 mL three-necked flask equipped with a mechanical stirrer, a condenser and a thermometer 1.8 g of 1-(3-hydroxymethyl pyridyl-2)-4-methyl-2-phenyl-piperazine are added to ~5 mL of concentrated sulfuric acid that was previously cooled to 10° C. The obtained solution is mixed at room temperature for 4 hours, then heated for one hour to about 50° to 60° C. After cooling, the reaction mass is added to 25 g of ice under mixing and neutralized with a concentrated ammonia solution or sodium hydroxide. The formed precipitate is separated by filtration. The mother liquor is evaporated to dryness under vacuum. Both the formed precipitate and the residue from the mother liquor are each suspended in ~20 mL of isopropanol. The combined isopropanol extracts are evaporated to dryness. An oil is obtained which contains 1.35 g of mirtazapine (yield 80%).

Example 3

Preparation of Mirtazapine

[0046] 1-(3-Hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine (1.8 g) is added to ~5 mL of concentrated sulfuric acid. The resulting solution is mixed at 35° C. for 6 hours. After cooling, the reaction mixture is added to 25 g of ice under mixing and basified with a concentrated ammonia solution or sodium hydroxide solution to pH=10. The separated precipitate is extracted into methylene chloride and the extract is evaporated to dryness; 1.6 g of Mirtazapine is obtained (yield 95%).

Example 4

Preparation of 1-(3-Carboxypyridyl-2-)-4-Methyl-2-Phenyl-Piperazine

[0047] 1-(3-cyanopyridyl-2-)-4-methyl-2-phenyl-piperazine (54 g) is dissolved in 340 mL of ethanol and 34 mL of water. Potassium hydroxide flakes, 85% (113 g), are added and the reaction mixture is heated in an autoclave to 140° C. The pressure increases to 3-4 atmospheres and the reaction mixture is maintained under pressure with mixing for 5 hours. After 5 hours, the reaction mixture is cooled, the ethanol is removed from the mixture by vacuum distillation, fresh water and toluene are added and the 2 phases are separated. The water solution is neutralized with hydrochloric acid (HCl) to pH=6.5-7. At pH=6.5-7 the water is evaporated and toluene is added. The inorganic salts are filtered and the toluene solution is evaporated to dryness yielding 52 g of 1-(3-carboxypyridyl-2-)-4-methyl-2-phenyl-piperazine (yield: 90%).

Example 5

Preparation of 1-(3-Carboxypyridyl-2-)-4-Methyl-2-Phenyl-Piperazine

[0048] Potassium hydroxide (150 g of KOH flakes, 85%) and 75 mL of water and 6.5 g of DMSO are added to 1-(3-cyanopyridyl-2-)-4-methyl-2-phenyl-piperazine (54 g) and the reaction mixture is heated to 145-150° C. and mixed for 8 hours. After 8 hours, the inorganic phase containing water and potassium hydroxide (KOH) is separated and the organic phase, containing mainly a product oil, is cooled. Fresh water and toluene are added and the two phases are separated. The aqueous solution is neutralized with HCl to pH=6.5-7. At pH=6.5-7, the water is evaporated and toluene is added. The inorganic salts are filtered and the toluene solution is evaporated to dryness yielding 52 g of 1-(3-carboxypyridyl-2-)-4-methyl-2-phenyl-piperazine (yield: 90%).

Example 6

Recrystallization of Mirtazapine

[0049] Mirtazapine (20 g), obtained as in Examples 2 and 3, is suspended in 20 mL of ethanol and heated to reflux. At reflux, 40 mL of water is added dropwise to the solution over one hour followed by cooling to 10° C. The resulting filter cake is washed with a solution of water:ethanol (2:1) and dried at 60° C. under a vacuum. Crystallized mirtazapine, 18 g, is obtained in 90% yield.

[0050] Table 1 sets forth a summary of additional experiments generally following procedures described above wherein the Yield % is the percent yield of mirtazapine crystals from crude mirtazapine and the Purity % is the percent purity as compared to a mirtazapine standard.

TABLE 1

Purification of Crude Mirtazapine by Recrystallization

Solvent system	Ratio of solvents ml:ml/g	Conditions	Yield[1] %
hexane	10	reflux	55
toluene	3	reflux	32
toluene	2	reflux	53
acetone/water	6:25	25° C.	65
ethanol/water	7:10	reflux	67
methanol/water	2.25:1.5	reflux	67
ethanol/water	1.5:2	reflux	72
isopropyl/water	1.65:2	reflux	60
acetone-water	3:2	reflux	53
ethanol/water	1:1.3	reflux	70
ethanol/water	1.3:1.75	reflux	90.3
ethanol/water	1:4	reflux	100
ethanol/water	1.1:1.2	reflux	87.8
ethanol/water	0.8:0.9	reflux	90
ethanol/water	0.8:1	reflux	57
ethanol/water	0.6:0.7	reflux	89.1
ethanol/water	0.35:0.7	reflux	91.5
ethanol/water	0.6:0.69	reflux	87
ethanol/water	2:2.8	reflux	95.6

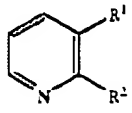
[1]g mirtazapine crystals 100%/g mirtazapine crude 100%

[0051] Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rule of law.

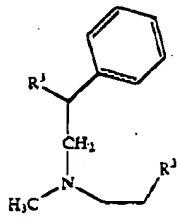
We claim:

1. A method for the preparation of mirtazapine, comprising the steps of:

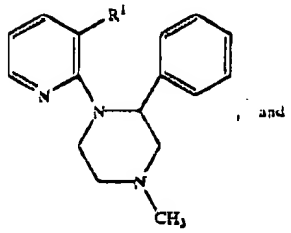
(a) reacting a compound of the formula



with a compound of the formula

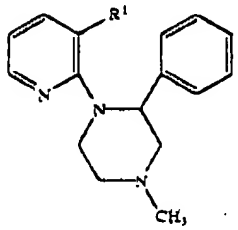


to form a compound of the formula



and

(b) adding a ring closing reagent to the compound of the formula



to form mirtazapine wherein R^1 is selected from the group consisting of hydroxymethyl, chloromethyl, bro-

momethyl and iodomethyl; R^2 is amine; and R^3 is selected from the group consisting of chloro, fluoro, bromo and iodo.

2. The method of claim 1, wherein R^1 is hydroxymethyl, R^2 is $—NH_2$, and R^3 is chloro.

3. The method of claim 1, wherein said a ring closing reagent is selected from the group consisting of sulfuric acid, concentrated sulfuric acid, concentrated hydrochloric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid, phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide, Lewis acids, aluminum chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride.

4. The method of claim 2, wherein said ring closing reagent is sulfuric acid.

5. The method of claim 1 which further comprises the step of heating.

6. A method for the preparation of mirtazapine, comprising the steps of:

(a) reacting 2-amino-3-hydroxymethyl pyridine with N-methyl-1-phenyl-2,2'-iminodiethyl chloride to form 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine, and

(b) adding a ring closing reagent to the 1-(3-hydroxymethylpyridyl-2)-4-methyl-2-phenyl-piperazine to form mirtazapine.

7. The method of claim 6, wherein said a ring closing reagent is selected from the group consisting of sulfuric acid, concentrated sulfuric acid, concentrated hydrochloric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid, phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide, Lewis acids, aluminum chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride.

8. The method of claim 6 wherein the ring closing reagent is sulfuric acid.

9. The method of claim 6 further comprising the step of heating.

10. A process for making 1-(3-carboxypyridyl-2)-4-methyl-2-phenyl-piperazine by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine comprising the step of reacting 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine with a base wherein the base is present in a ratio of up to about 12 moles of the base per one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine.

11. The process of claim 10 wherein the ratio of the base to 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine is about 12 moles of base to about one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine to about 9 moles of base to about one mole of 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine.

12. The process of claim 10 wherein the base is potassium hydroxide or sodium hydroxide

13. The process of claim 12 wherein the mixture of the 1-(3-cyanopyridyl-2)-4-methyl-2-phenyl-piperazine and the base is heated to at least about 130° C.

14. The process of claim 13 wherein the mixture is heated to about 130° C. to about 150° C.

15. The process of claim 12 wherein the hydrolysis is carried out in water and an aprotic polar solvent.

16. The process of claim 12 wherein the hydrolysis is carried out in a mixture of water and a solvent selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanol, dimethylformamide, dimethylacetamide and dimethylsulfoxide.

17. The process of claim 12 wherein the hydrolysis is carried out at a pressure of about 3 to about 4 atmospheres pressure.

18. The process of claim 12 wherein the hydrolysis is carried out at almost neat conditions.

19. A process for recrystallized mirtazapine from crude mirtazapine comprising the steps of:

(a) heating a mixture of crude mirtazapine and a solvent;

(b) cooling the mixture such that purified mirtazapine precipitatis; and

(c) isolating the recrystallized mirtazapine.

20. The process of claim 19 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, acetone, and mixtures thereof.

21. The process of claim 20 further comprising the step of adding water to the mixture of mirtazapine and solvent to facilitate precipitation of mirtazapine.

22. The process of claim 19 where in the solvent is selected from the group consisting of toluene, hexane, and methylene chloride, and mixtures thereof.

23. The process of claim 20 wherein the solvent is ethanol.

24. The process of claim 19 wherein the recrystallized mirtazapine is a mirtazapine water adduct.

25. The product of the process claim 24.

26. Mirtazapine prepared according to the process of claim 1.

27. A pharmaceutical composition comprising a therapeutically effective amount of mirtazapine of claim 26, and a pharmaceutically acceptable carrier.

28. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 27.

* * * * *

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PAT NO.:

- ☐ New Application with Transmittal Letter
- ☐ Utility ☐ Design ☐ CIP ☐ PCT ☐ Provisional
- ☐ Filing Under 37 CFR 1.53(b) ☐ CONT ☐ DIV
- ☐ Filing Under 37 CFR 1.53(d) (CPA)
- ☒ Filing Under 37 CFR 1.114(RCE) (copy)
- ☐ Specification Consisting of: _____ pages
- ☐ Combined Declaration & Power of Attorney
- ☐ Assignment / Cover Letter
- ☐ Letter to Official Draftsman
- ☐ Drawings ___ Sheets ☐ Formal ☐ Informal ☒ Red-line
- ☐ Completion of Filing Requirements, PCT/DO/EO/[illegible] or Formalities Letter and Executed Declaration
- ☐ Priority Document(s) / Cover Letter, No. Doc. _____
- ☐ Amendment: _____
  - ☐ Transmtl Ltr ☐ Large Entity ☐ Small Entity
- ☐ Response _____
- ☒ Information Disc Stmnt. PTO-1449(s) 1 ref(s) (copy)
- ☐ Notice of Appeal ☐ Appeal Brief
- ☐ Issue Fee Transmittal
- ☐ FEES: _____
- ☒ Letter: re resubmitting copies of papers 3-19-02
- ☒ Other: filed by hand carry
  copy of Pkg. for Cons. of IDS
  Petition, under 37 CFR 1.313(c)(2).

Receipt is hereby acknowledged of the papers filed as indicated in connection with the above identified case. stamped postcard receipt.
COMMISSIONER OF PATENTS AND TRADEMARKS
Due Date: _____
Handcarry: Petitions Office, Crystal Plaza 4, Room 3C-23

02 MAR 20 PM 3:32 RECEIVED

DOCKET NO. 1422-449P